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Welfare versus Autonomy in Human Subjects Research

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WELFARE VERSUS AUTONOMY IN HUMAN SUBJECTS RESEARCH

MARK S. STEIN*
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ABSTRACT

Autonomy is commonly seen as a fundamental value that should guide the federal regulation of human subjects research. In this Article, we argue that autonomy is compromised, and should be compromised, for the sake of the welfare of research subjects and the welfare of people who stand to benefit from medical research. Such a compromise of autonomy is evident in regulatory exceptions to the requirement of informed consent, including the exceptions for emergency research and minimal-risk research. Less obviously, the blind clinical trial inherently represents a compromise of autonomy, as subjects are offered medical treatment on the condition that they give up (1) the right to know what treatment they are receiving, and (2) the right to participate in decisionmaking about their treatment. While such an offer of treatment conditioned on a waiver of informed-consent rights does not contravene the libertarian conception of autonomy, it does contravene the liberal conception of autonomy that is now dominant in bioethics. Autonomy is also compromised, on both the liberal and libertarian accounts, when access to experimental drugs is limited in order to channel people who are seeking those drugs into clinical trials.

We endorse most of the ways in which the regulation of human subjects research compromises autonomy for the sake of welfare. We also suggest some ways in which autonomy should be further subordinated to welfare, especially in the selection of research subjects. Researchers should select subjects who present a more favorable risk/benefit ratio, even if those subjects are less able to give autonomous consent. The necessity for this rule is illustrated by the Gelsinger case. In that case, researchers initially sought to test a gene-therapy treatment on terminal infants. They were persuaded instead to test the treatment on adults with a mild form of the disease, since those adults could give fully autonomous consent. One young adult subject died as a result; he would not have died if autonomy had been properly subordinated to welfare.

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I. INTRODUCTION

Autonomy is commonly seen as a fundamental value that should guide the federal regulation of human subjects research. In this Article, we argue that the autonomy of research subjects is compromised, and should be compromised, for the sake of the welfare of research subjects and the welfare of people who will benefit from medical research. Our arguments are both positive (descriptive) and normative. We describe ways in which autonomy is compromised for the sake of welfare, and we endorse those aspects of the federal regulatory scheme. However, we do not believe that the balance is perfect. In some respects, autonomy should be compromised even further.

In Part II of this Article, we offer a preliminary discussion of the values of autonomy and welfare in the context of the federal regulations governing human subjects research.¹ We distinguish between the liberal conception of autonomy and the libertarian conception of autonomy. The liberal conception emphasizes informed consent, while the libertarian conception opposes coercive or fraudulent interference with personal decisions. The liberal conception is dominant in bioethics and is reflected in the federal regulations,² but the libertarian conception has influential advocates as well. In the regulation of human subjects research, autonomy is sometimes compromised more on one conception than on the other.

In Part III, we discuss the way in which restrictive drug laws channel people into volunteering to be subjects in clinical trials.³ When the law restricts access to experimental drugs in order to populate clinical trials, it compromises the autonomy of patient volunteers for the sake of the beneficiaries of research. Objections to restrictive drug laws generally come from libertarians, but these laws actually compromise autonomy more severely under the liberal conception of autonomy: liberals often condemn inducements to become a research subject that fall far short of actual coercion.

1. See 45 C.F.R. pt. 46 (2010); 21 C.F.R. pts. 50, 56 (2010).

2. See, e.g., 45 C.F.R. § 46.116; 21 C.F.R. § 50.20 (basic informed-consent provisions).

3. See, e.g., 21 U.S.C. § 360bbb(b)(3) (2006) (requiring that “the investigational drug or investigational device will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval”); 21 U.S.C. § 360bbb(c)(5) (requiring that “the investigational drug or investigational device will not interfere with the enrollment of patients in ongoing clinical investigations”).

In Part IV, we consider two regulatory exceptions to the requirement of informed consent: the exceptions for emergency research⁴ and minimal-risk research.⁵ Once again, these exceptions compromise the autonomy of the subjects of research for the sake of the beneficiaries of research. Probably the only way to deny that the emergency-research and minimal-risk exceptions compromise autonomy is to adopt a theory of hypothetical consent as satisfying the dictates of autonomy. The hypothetical-consent approach, however, is contrary to the liberal conception of autonomy, as the liberal conception has a strong default presumption against experimentation. The hypothetical-consent approach might be acceptable under a libertarian conception of autonomy, but even there it is questionable.

In Part V, we argue that the blind clinical trial inherently represents a compromise of autonomy. In the blind clinical trial, subjects are offered medical treatment on the condition that they give up (1) the right to know what treatment they are receiving, and (2) the right to participate in decisionmaking about their treatment. While such an offer of treatment conditioned on a waiver of informed-consent rights does not contravene the libertarian conception of autonomy, it does contravene the dominant liberal conception of autonomy.

In all of the foregoing areas—the channeling of patients into clinical trials, regulatory exceptions to informed consent, and the required waiver of informed-consent rights that is inherent in the blind clinical trial—we endorse the compromise of autonomy for welfare.

In Part VI, we consider the conflict between welfare and autonomy in the selection of research subjects. Here, autonomy is compromised for the sake of welfare to some extent, but welfare may also be compromised for the sake of autonomy. The regulations impose paternalistic limitations on the selection of subjects, compromising the autonomy of some would-be subjects by excluding them from experiments for the sake of their own welfare.⁶ Regrettably, however, the regulations do not explicitly favor the selection of the subject group with the best risk/benefit ratio. In cases where members of the group with the best risk/benefit ratio cannot give fully autonomous consent, the regulations may actually disfavor selection of that group.⁷

In the area of subject selection, autonomy should be further subordinated to welfare, as illustrated by the tragic Gelsinger case.⁸ In that case, researchers initially sought to test a gene-therapy treatment on terminal infants. They were persuaded instead to test the

4. 21 C.F.R. § 50.24; 61 Fed. Reg. 51,531 (Oct. 2, 1996) (codified at 45 C.F.R. pt. 46).

5. 45 C.F.R. § 46.116(d).

6. See 45 C.F.R. § 46.111(a)(2); 21 C.F.R. § 56.111(a)(2).

7. See 45 C.F.R. § 46.111(a)(3); 21 C.F.R. § 56.111(a)(3).

8. See generally Julian Savulescu, *Harm, Ethics Committees and the Gene Therapy Death*, 27 J. MED. ETHICS 148 (2001).

treatment on adults with a mild form of the disease, since those adults could give fully autonomous consent.⁹ One young adult subject died as a result; he would not have died if autonomy had been properly subordinated to welfare.¹⁰

Although our arguments in this Article are both descriptive and normative, we believe that the Article's chief contributions are its descriptive analysis of the conflict between welfare and autonomy and its elucidation of the distinction between liberal autonomy and libertarian autonomy. Readers may be surprised by the extent to which autonomy is subordinated to welfare in the regulation of human subjects research. On the other hand, it will probably surprise no one that two theorists sympathetic to welfarism take the welfarist side in normative questions. In presenting our normative positions, we are sometimes content merely to show how welfare is opposed to autonomy, and to invite readers to share our welfarist judgments.

II. WELFARE AND AUTONOMY IN THE FEDERAL REGULATIONS

The values of welfare and autonomy are overlapping, vague, and contested. In this Part, we explore these values in the context of the federal regulations that govern most human subjects research in the United States. There are two important sets of regulations, which we will refer to as the Department of Health and Human Services (HHS) regulations and the Food and Drug Administration (FDA) regulations.¹¹ The FDA regulations govern research on products regulated by the FDA.¹² The HHS regulations govern research conducted by the federal government, research that is federally funded, and research conducted by institutions that have accepted the regulations as binding even as to nonfunded research.¹³ The FDA regulations on human subjects research are for the most part identical to subparts A and D of the HHS regulations.¹⁴ Many studies are subject to both the FDA regulations and the HHS regulations.

9. *Id.* at 148.

10. *Id.*

11. This terminology is somewhat problematic, as the FDA is an agency within the HHS. But the FDA itself uses this terminology, see FDA, Comparison of FDA and HHS Human Subject Protection Regulations, <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/EducationalMaterials/ucm112910.htm> (last visited Mar. 18, 2011), and it is probably more accurate than alternatives. The HHS regulations are often referred to as the "Common Rule" because a number of agencies have adopted part or all of the HHS regulations verbatim. However, only subpart A is actually common to all the other agencies, and we will be referring at times to other parts of the HHS regulations.

12. 21 C.F.R. § 50.1(a).

13. 45 C.F.R. § 46.101(a); see, e.g., CARL H. COLEMAN ET AL., THE ETHICS AND REGULATION OF RESEARCH WITH HUMAN SUBJECTS 107 (2005).

14. Subpart D of the HHS regulations governs experimentation on children; it is essentially duplicated in subpart D of the FDA regulations. See 45 C.F.R. §§ 46.401-46.409; 21 C.F.R. §§ 50.50-50.56. Not duplicated in the FDA regulations are subpart C of the HHS

The federal regulation of human subjects research largely operates through requirements directed at institutional review boards (IRBs). Some of these requirements appear to express a welfarist command, while others are associated with the value of autonomy.

A. Overview of Criteria for IRB Approval of Research

Section 46.111 of the HHS regulations is titled “Criteria for IRB approval of research.”¹⁵ Section 46.111(a)(2) states the requirement that “[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.”¹⁶ This appears to be a welfarist criterion. Risks to subjects must be balanced against the benefits both to subjects and to others who may benefit from the research. Greater benefits can justify greater risks. Another essentially welfarist provision of the regulations is section 46.111(a)(1), which requires that “[r]isks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.”¹⁷

The regulations most clearly reflect the value of autonomy in imposing requirements of informed consent. Section 46.111(a)(4) of the HHS regulations requires, as a condition of IRB approval of research, that “[i]nformed consent will be sought from each prospective subject or the subject’s legally authorized representative, in accordance with, and to the extent required by §46.116.”¹⁸ Accordingly, 45 C.F.R. § 46.116 states:

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.¹⁹

regulations, regarding prisoners, and subpart B, regarding pregnant women, neonates, and fetuses. Where the HHS regulations and the FDA regulations are substantially identical, we will refer to the HHS provision in the text and cite to both provisions in the notes.

15. 45 C.F.R. § 46.111. The parallel provision in the FDA regulations is 21 C.F.R. § 56.111.

16. HHS, 45 C.F.R. § 46.111(a)(2); FDA, 21 C.F.R. § 56.111(a)(2).

17. HHS, 45 C.F.R. § 46.111(a)(1); FDA, 21 C.F.R. § 56.111(a)(1).

18. HHS, 45 C.F.R. § 46.111(a)(4); FDA, 21 C.F.R. § 56.111(a)(4).

19. HHS, 45 C.F.R. § 46.116; *see also* FDA, 21 C.F.R. § 50.20.

This section goes on to list the information that must be provided to a prospective subject. The regulations also contain exceptions to the requirement of informed consent, some of which are discussed in Part IV below.

Another regulatory criterion for IRB approval of research is that the selection of subjects be “equitable.”²⁰ Section 46.111(a)(3) provides that in making the assessment of whether selection is equitable:

[T]he IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.²¹

As discussed below in Part VI, this provision evinces some preference for selecting subjects who can make an autonomous choice. To that extent, it also reflects the value of autonomy.

B. What is Autonomy?

We have been using the terms autonomy and welfare, and it is now time to look at these concepts more closely. Autonomy is an extremely slippery concept. Perhaps at the core of the concept of autonomy is the idea that people should be able to rule themselves rather than be ruled by others. However, there are many different conceptions of autonomy. We believe it is useful to distinguish between two broad conceptions, or families of conceptions, both of which will concern us in what follows: the liberal conception and the libertarian conception. The liberal conception is dominant in bioethics and is reflected in the federal regulations. The libertarian conception is an important alternative that is prominent in other areas of the law, and that has some followers in bioethics as well.

Under the libertarian conception, government or private actors violate autonomy when they interfere, through force or fraud, with a person making his or her own decisions, unless those decisions would violate the rights of others. The libertarian conception of autonomy rejects paternalistic interference—interference that purports to be for the person’s own good—as well as interference motivated by other goals.

The dominant liberal conception of autonomy also condemns force and fraud. But the liberal conception endorses a degree of paternalism that sets it apart from the libertarian conception.

20. HHS, 45 C.F.R. § 46.111(a)(3); FDA, 21 C.F.R. § 56.111(a)(3).

21. HHS, 45 C.F.R. § 46.111(a)(3); FDA, 21 C.F.R. § 56.111(a)(3).

Informed consent is a liberal principle, not a libertarian principle. The requirement that consent be informed is a form of paternalism; liberal autonomy will not honor a person's decision to be a subject in an experiment unless that decision is made with full information, under conditions that conduce to full understanding and authentic choice. Libertarian autonomy, of course, endorses the requirement of consent, in human subjects research as in other social endeavors. However, libertarian autonomy cannot easily endorse the requirement of *informed* consent. Libertarianism respects the actual choices of people, whether or not those choices are made with full information; libertarianism will not disregard the actual choices of people in a search for authentic choice. Libertarianism can endorse a requirement of informed consent, if at all, only as a prophylactic measure, to prevent fraudulent inducement.

The influential text *Principles of Biomedical Ethics*,²² by Professors Tom Beauchamp and James Childress, is squarely in the liberal camp. Beauchamp and Childress write that “[p]ersonal autonomy encompasses, at a minimum, self-rule that is free from both controlling interference by others and from certain limitations such as an inadequate understanding that prevents meaningful choice.”²³ Further, “[t]o respect autonomous agents . . . requires more than noninterference in others’ personal affairs. It includes, in some contexts, building up or maintaining others’ capacities for autonomous choice while helping to allay fears and other conditions that destroy or disrupt autonomous action.”²⁴

Also squarely in the liberal camp is the Belmont Report, the 1979 report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.²⁵ The federal regulations governing human subjects research are based in part on this report. The Belmont Report is somewhat idiosyncratic in using the term “respect for persons” in place of “autonomy.” Like most other bioethicists, we prefer the term “autonomy.”²⁶

We take Robert Nozick to be emblematic of libertarianism (the Nozick of *Anarchy, State, and Utopia*,²⁷ as opposed to the Nozick of

22. TOM L. BEAUCHAMP & JAMES F. CHILDRESS, *PRINCIPLES OF BIOMEDICAL ETHICS* (6th ed. 2009).

23. *Id.* at 99.

24. *Id.* at 103.

25. NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, *ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH* (1979) [hereinafter Belmont Report], available at <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>.

26. The term “respect for persons” is too general. Many principles can claim to be founded on a respect for persons, including utilitarianism. See, e.g., R.M. HARE, *MORAL THINKING: ITS LEVELS, METHOD AND POINT* (1981).

27. ROBERT NOZICK, *ANARCHY, STATE, AND UTOPIA* (1974).

The Examined Life).²⁸ Nozick is not particularly known for his views on bioethics, but that does not really matter: libertarians generally do not see bioethics as a special topic meriting special rules. Contemporary exponents of a libertarian approach to bioethics include Professors Richard Epstein²⁹ and Eugene Volokh.³⁰

While we believe that the liberal/libertarian distinction is illuminating, it does not explain every dispute over the nature of autonomy. For example, the issue of whether hypothetical consent can satisfy autonomy, considered in Part IV, does not precisely track the liberal/libertarian divide. Also, the two camps are not monolithic. There are differences among liberals and differences among libertarians.

One heterodox libertarian view is that of Professors Cass Sunstein and Richard Thaler, who advocate what they call “libertarian paternalism.”³¹ To us it seems that Sunstein and Thaler often advocate policies that are *more* libertarian than some available alternatives, but that are not actually libertarian. It is not our role to police those who want to use the libertarian label, but we will continue, for our own purposes, to draw a relatively sharp distinction between libertarianism and liberalism, key to which is the libertarian attitude of antipaternalism.

Our discussion of specific issues in subsequent parts of this Article will illuminate the distinction between liberal autonomy and libertarian autonomy. Readers can then decide whether the distinction is useful and has been convincingly deployed. We believe we are the first to deploy this distinction in a sustained fashion in the context of human subjects research.

C. *The Place of Autonomy and the Theoretical Basis of Informed Consent*

There are a number of ways of understanding the place of autonomy in bioethics and the theoretical basis of the principle of informed consent. First, autonomy can be seen as a fundamental value that underlies the principle of informed consent and constrains the pur-

28. ROBERT NOZICK, *THE EXAMINED LIFE* 286-87 (1989) (“The libertarian position I once propounded now seems to me seriously inadequate . . .”). By the end of his life, Nozick may have returned to libertarianism. See ROBERT NOZICK, *INVARIANCES* 263, 281-82 (2001).

29. See, e.g., Richard A. Epstein, *The Erosion of Individual Autonomy in Medical Decisionmaking: Of the FDA and IRBs*, 96 GEO. L.J. 559 (2008) [hereinafter Epstein, *The Erosion of Individual Autonomy in Medical Decisionmaking*]; Richard A. Epstein, *Contractual Principle Versus Legislative Fixes: Coming to Closure on the Unending Travails of Medical Malpractice*, 54 DEPAUL L. REV. 503 (2005).

30. See, e.g., Eugene Volokh, *Medical Self-Defense, Prohibited Experimental Therapies, and Payment for Organs*, 120 HARV. L. REV. 1813 (2007).

31. RICHARD H. THALER & CASS R. SUNSTEIN, *NUDGE: IMPROVING DECISIONS ABOUT HEALTH, WEALTH, AND HAPPINESS* (2008); Cass R. Sunstein & Richard H. Thaler, *Libertarian Paternalism Is Not an Oxymoron*, 70 U. CHI. L. REV. 1159 (2003).

suit of social welfare. This fundamental-constraint view of autonomy is similar to the way rights are often conceived in other contexts.

A second view sees autonomy not as an absolute constraint, but as one fundamental value in a pluralist system. Under the pluralist view, autonomy must sometimes bow to social welfare, and social welfare must sometimes bow to autonomy; neither value is supreme. The pluralist view agrees with the fundamental-constraint view in seeing autonomy as a fundamental value, but disagrees that autonomy is an absolute constraint. While the pluralist view may be less familiar to those outside the field of bioethics, it is very widely held, perhaps dominant, among bioethicists.³²

Those who hold to a liberal conception of autonomy are generally pluralists. Advocates of liberal autonomy generally do not oppose all policies that compromise liberal autonomy. They may support a policy that compromises autonomy if it serves some other important value, such as welfare.

A third view of the place of autonomy, to which we are somewhat sympathetic, claims that autonomy is not a fundamental value at all. Rather, autonomy is a purely instrumental value that serves to promote the welfare of research subjects. Under this view of autonomy as a welfare-promoting instrumental value, informed consent requirements are justified as a means of protecting research subjects from an undue risk of harm (subjects being less likely to give informed consent to research that poses such an undue risk of harm).

The value of autonomy is so often taken as fundamental that it may seem odd to suggest that the ultimate justification for autonomy and informed consent may be welfarist. However, a welfarist grounding for consent requirements would have seemed less odd to those who first promulgated those requirements. As Beauchamp and Childress remark, “[t]hroughout the early history of concern about research subjects, consent requirements were proposed primarily as a way to minimize the potential for harm.”³³

Our thesis that autonomy is and should be compromised for the sake of welfare entails a rejection of the view of autonomy as an absolute constraint on the pursuit of social welfare, both as a description of the nature of human subjects regulation and as a normative view as to how research should be regulated. However, nothing in this Article

32. See, e.g., BEAUCHAMP & CHILDRESS, *supra* note 22; Belmont Report, *supra* note 25.

33. BEAUCHAMP & CHILDRESS, *supra* note 22, at 118. They go on to note that “since the mid-1970s the primary justification advanced for requirements of informed consent has been to protect autonomous choice, a loosely defined goal that institutions often bury in broad statements about protecting the rights of patients and research subjects.” *Id.*; see also JESSICA W. BERG ET AL., INFORMED CONSENT 18 (2d ed. 2001) (“The primary goals of informed consent are the protection of patient or subject welfare and the promotion of autonomy . . .”).

entails a rejection of the pluralist view of autonomy, the view that autonomy is one fundamental value among others. On each of the issues we address we come down on the welfarist side, but we do not seek to establish that autonomy should never prevail against welfare. Nor do we argue, as a descriptive matter, that the regulation of human subjects research *is* now fully welfarist, so that welfare is never compromised for the sake of autonomy. As discussed in Part VI, welfare may be compromised for the sake of autonomy to some extent.

Though our argument is consistent with *a* pluralist view, we attempt to move the discussion farther *toward* the pole of welfare. Much of what we say will challenge specific views held by many pluralists, if not their overall outlook.

D. What is Welfare?

There are three leading conceptions of welfare: the hedonic account, the informed-preference account, and the objective-list account.³⁴ Under the hedonic account, positive welfare is a positive mental state or subjective experience, such as happiness or enjoyment; negative welfare is a negative mental state such as unhappiness or suffering. Under the informed-preference account, positive welfare is the satisfaction of informed preferences, while negative welfare is the frustration of informed preferences.

The objective-list account of welfare is less well-defined, and there is some question as to whether it is a welfarist position at all. Under the objective-list account, a thing *X* can contribute to a person's welfare even though the person does not experience *X* as good. Despite its name, the objective-list account is only partly objective; those who consider themselves welfarists never adopt a conception of welfare that is totally divorced from subjective experience.

One argument we advance in this Article is that the federal regulations on human subjects research sometimes compromise (and should compromise) a subject's autonomy for the sake of the subject's own welfare. It might be thought that such an argument cannot be advanced based on the informed-preference account of welfare. The informed-preference account of welfare, it might be thought, must be identical to the informed-consent account of autonomy, so that if a person has given informed consent to be a subject, or is willing to do so, that can never be contrary to her welfare on the informed-preference account of welfare—at least, it can never be contrary to her welfare *ex ante*. Therefore, it might be thought, if we say a subject's autonomy is compromised for the sake of the subject's own welfare, we must hold to some alternative account of welfare, such as the

34. See L. W. SUMNER, WELFARE, HAPPINESS, AND ETHICS (1996); ROBERT E. GOODIN, UTILITARIANISM AS A PUBLIC PHILOSOPHY 12-16 (1995); JAMES GRIFFIN, WELL-BEING (1986).

hedonic account (or an objective-list account that includes a hedonic element).

There is something to this line of reasoning. It is easier to see how a subject's autonomy can be compromised for the sake of her welfare on the hedonic account of welfare than on the informed-preference account of welfare. And indeed, the federal regulations do seem somewhat more consistent with the hedonic account of welfare than with the informed-preference account. Nevertheless, the informed-preference account of welfare is not precisely identical to the informed-consent account of autonomy; the informed-preference account of welfare is generally more idealized. For example, a preference between two courses of action may not be considered fully informed unless it is the preference that the chooser would have if she could, counterfactually, experience the consequences of both courses of action, and then choose between them. So it is possible to compromise a subject's autonomy for the sake of her welfare, even if we adopt both an informed-consent account of autonomy and an informed-preference account of welfare.

The Belmont report uses the term "beneficence" in place of "welfarism," to describe the basic ethical principle giving rise to the rules "do not harm" and "maximize possible benefits and minimize possible harms."³⁵ Once again, we do not adopt that usage. "Beneficence" is a more general and slightly more idiosyncratic term than "welfarism." Beneficence could embrace benefits other than welfare; for example, knowledge itself could be considered a benefit, regardless of its effects on welfare. Under such a nonwelfarist principle of beneficence, one could say that it is reasonable to risk harm to the welfare of subjects even if the welfare losses to subjects are not balanced by welfare gains to nonsubjects, but only by increased knowledge in the abstract. Section 45 C.F.R. § 46.111(a)(2) of the HHS regulations is itself susceptible to this interpretation, though we doubt many would embrace it. In any event, we use the term "welfarism," rather than "beneficence," because we believe that welfarism more accurately describes the meaning of the regulations and (even if it did not) because welfarism more accurately describes our own normative approach.

E. From Individual Welfare to Social Welfare

The most prominent welfarist theory of justice, and one for which we have considerable sympathy, is utilitarianism. The utilitarian theory of justice directs that welfare be maximized, with equal weight given to the welfare of everyone.³⁶ Social welfare, according to

35. Belmont Report, *supra* note 25.

36. See MARK S. STEIN, *DISTRIBUTIVE JUSTICE AND DISABILITY* 33-35 (2006); PETER SINGER, *PRACTICAL ETHICS* 21 (2d ed. 1993); JOHN C. HARSANYI, *ESSAYS ON ETHICS, SOCIAL*

utilitarianism, is simply the unweighted sum (or average) of individual welfare. Thus, 45 C.F.R. § 46.111(a)(2) of the HHS regulations, with its command to balance risks and benefits, seems utilitarian in spirit.³⁷

There are also more egalitarian welfarist theories. While utilitarianism gives equal weight to the welfare of everyone, more egalitarian welfarist theories (ironically) do not give equal weight to the welfare of everyone; they give extra weight to the welfare of people who have less welfare.³⁸ For ease of analysis, we will assume a utilitarian approach that does not give extra weight to the welfare of those who are worse off. We believe that our analysis should also be of interest to those who hold more egalitarian welfarist views.

In the regulation of human subjects research, the issue of whether extra weight should be given to the welfare of those who are worse off is perhaps less relevant than the issue of whether extra weight should be given to the welfare of the subjects of research. By requiring that risks to subjects be reasonable “in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result,”³⁹ 45 C.F.R. § 46.111(a)(2) requires that a balance be struck between the welfare of subjects and the welfare of the beneficiaries of research (most of whom are not subjects). Some might believe that it is never justified to compromise the expected welfare of subjects in order to increase the welfare of the beneficiaries of research; such a view would be contrary to 45 C.F.R. § 46.111(a)(2). Others might believe that in striking the balance between subject welfare and beneficiary welfare, the welfare of subjects should matter more, as a fundamental matter, than the welfare of beneficiaries. Such a subject-weighted welfarist approach could be consistent with the regulatory scheme.

A welfarist approach that gives greater weight to the welfare of subjects than to the welfare of beneficiaries might seem to be contrary to utilitarianism, since utilitarianism gives equal weight to the welfare of each. In fact, the issue is more complicated. As a matter of fundamental ethics, utilitarianism cannot value the welfare of subjects more than the welfare of beneficiaries. As a matter of practice, however, utilitarianism does counsel IRBs to give more weight to subject welfare than nonsubject welfare. If the welfare of subjects is not sufficiently protected, people will not volunteer to be subjects. So an experiment that costs the life of one subject and saves the lives of

BEHAVIOR, AND SCIENTIFIC EXPLANATION 72 (Gerald Eberlein & Werner Leinfellner eds., 1976).

37. It does not necessarily reflect a thoroughgoing utilitarianism.

38. See generally STEIN, *supra* note 36.

39. HHS, 45 C.F.R. § 46.111(a)(2) (2010); see also FDA, 21 C.F.R. § 56.111(a)(2) (2010).

two nonsubjects could easily be bad for social welfare if it discourages people from becoming subjects in future experiments.⁴⁰

The balance between subject welfare and beneficiary welfare is an important issue in research ethics, but one that we, for the most part, do not address in this Article. We are interested in the opposition between autonomy and social welfare, whether social welfare is determined by subject welfare, nonsubject welfare, or both.

F. Welfare Versus Autonomy

As previously indicated, the value of welfare overlaps with the value of autonomy. The principle of informed consent, and the value of autonomy itself, can be seen as instrumental to welfare. Therefore, the conflicts between welfare and autonomy are not easy to tease out. It is wrong, for example, to think the mere requirement of informed consent shows that autonomy has prevailed over welfare, as the requirement of informed consent can be justified on welfarist grounds.

One way of posing the conflict between welfare and autonomy is through farfetched hypothetical examples. Suppose that one person's body has unique properties such that researchers can find a cure for cancer (all cancers) through use of his tissues. Unfortunately, the necessary experiments cannot be done without killing the prospective subject, and he is unwilling to volunteer. In this highly imaginary situation, we believe it would be right to conscript the subject, killing him but saving millions of others.⁴¹ Others may have a different intuitive response.

Such imaginary cases have their place, and we have given them a place in our prior work. But questions are bound to linger, even though we attempt to stipulate them away. How do we know that experimenting on this unfortunate individual will yield a cure for cancer? Why is it necessary to kill him? If his tissues are so scientifically valuable, wouldn't it be better to leave him alive?

In the example as given, the good that can be done is so enormous that it tends to wash out such doubts. But if we start to reduce the number of people who can be saved, the lingering questions gain force and can render the example, in our view, an illegitimate test of moral intuitions.

Imaginary cases are well deployed, from a welfarist perspective, in the work of Professors Louis Kaplow and Steven Shavell. In their book *Fairness Versus Welfare*,⁴² Kaplow and Shavell demonstrate

40. We believe there are also other instrumental reasons to elevate subject welfare, but we will not explore them here.

41. In this example, social welfare is opposed to both autonomy and to subject welfare.

42. LOUIS KAPLOW & STEVEN SHAVELL, *FAIRNESS VERSUS WELFARE* (2002). Our title is an *homage* to Kaplow and Shavell (*i.e.*, a rip-off).

that notions of fairness that depart from welfarism can, in a highly stylized hypothetical setting, reduce the welfare of everyone. Autonomy, under either a liberal conception or a libertarian conception, is a notion of fairness that can depart from welfarism. Therefore, it should be possible to deliver a Kaplow-Shavellian critique of autonomy in human subjects research, using examples such as they offer in their book.⁴³

We have chosen not to do so. While we make use of the occasional simplifying assumption and hypothetical case, in the main we present actual conflicts between welfare and autonomy for the judgment of the reader. This normative approach dovetails better with our descriptive project. And while it can be hard to tease out the actual conflicts between welfare and autonomy, there is doubtless something to be said for basing normative judgments on real-world situations rather than on imaginary cases.

III. CHANNELING SUBJECTS INTO CLINICAL TRIALS

We begin by considering the way in which restrictive drug laws channel medical patients into clinical trials of new drugs. The FDA oversees a lengthy drug-approval process, including at least three phases of human trials. The Federal Food, Drug, and Cosmetic Act (FDCA) generally prohibits the sale of new drugs that have not been approved by the FDA.⁴⁴ The restriction of access to unapproved drugs may be experienced as burdensome by terminally ill patients who may believe that an unapproved drug offers their only chance of survival. There are some avenues to expanded access, discussed below, but access is still limited, even for the terminally ill.

In *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*,⁴⁵ the plaintiffs mounted a constitutional challenge to the system of restricted access to unapproved drugs. The case received a great deal of attention when a three-judge panel of the D.C. Circuit accepted the plaintiffs' view that there was a constitutional right of access by the terminally ill to experimental drugs that had passed Phase I safety testing, but had not yet been approved by the FDA.⁴⁶

43. Some of the real conflicts we discuss seem not to lend themselves to hypothetical treatment as well as the examples discussed by Kaplow and Shavell, but that may be a failure of imagination on our part.

44. 21 U.S.C. § 355(a) (2006).

45. 495 F.3d 695 (D.C. Cir. 2007) (en banc).

46. *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 445 F.3d 470, 486 (D.C. Cir. 2006), *rev'd en banc*, 495 F.3d 695 (D.C. Cir. 2007). For commentary supporting the initial panel decision, see Volokh, *supra* note 30; Alissa Puckett, Comment, *The Proper Focus for FDA Regulations: Why The Fundamental Right to Self-Preservation Should Allow Terminally Ill Patients With No Treatment Options to Attempt to Save Their Lives*, 60 SMU L. REV. 635 (2007). For commentary opposing the initial panel decision, see Peter D. Jacobson & Wendy E. Parmet, *A New Era of Unapproved Drugs: The*

However, this temporary victory for the plaintiffs was reversed by the court en banc, which held that there was no constitutional right of access to unapproved drugs.⁴⁷

The system of restricted access to unapproved drugs compromises the autonomy of medical patients both for their own sake (a paternalistic restriction) and also for the sake of future patients who may benefit from the promotion of drug research through the clinical-trial system. We are more concerned with the research-based justification for restricted access, but we will first review the paternalistic justification.

The regulation of drugs reflects the paternalistic view that people would make worse decisions about drugs if drugs were unregulated. We assume that this paternalistic view is correct: people really are better off, on average, than they would be under a system of unregulated drugs. On that assumption, we have no problem endorsing the regulation of drugs.⁴⁸

Many feel that paternalistic drug regulation is less justified with respect to the terminally ill, because the terminally ill have less to lose. But as the Supreme Court explained in *United States v. Rutherford* (the Laetrile case),⁴⁹ there is a place for paternalism even with respect to the terminally ill:

[T]he concept of safety . . . is not without meaning for terminal patients For the terminally ill, as for anyone else, a drug is unsafe if its potential for inflicting death or physical injury is not offset by the possibility of therapeutic benefit Moreover, there is a special sense in which the relationship between drug effectiveness and safety has meaning in the context of incurable illnesses [I]f an individual suffering from a potentially fatal disease rejects conventional therapy in favor of a drug with no demonstrable curative properties, the consequences can be irreversible The FDA's practice also reflects the recognition, amply supported by expert medical testimony in this case, that with diseases such as cancer it is often impossible to identify a patient as terminally ill except in retrospect.

. . . Since the turn of the century, resourceful entrepreneurs have advertised a wide variety of purportedly simple and painless cures for cancer [T]his historical experience . . . suggest[s] why Congress could reasonably have determined to protect the

Case of Abigail Alliance v. Von Eschenbach, 297 JAMA 205 (2007); Daniel Meron, *Legal Developments Relevant to FDA Authority*, 62 FOOD & DRUG L.J. 441 (2007); Ezekiel J. Emanuel, *Drug Addiction*, NEW REPUBLIC, July 3, 2006, at 9.

47. *Abigail Alliance*, 495 F.3d at 713.

48. Some libertarians do object. See Epstein, *The Erosion of Individual Autonomy in Medical Decisionmaking*, *supra* note 29, at 573-74.

49. 442 U.S. 544 (1979).

terminally ill, no less than other patients, from the vast range of self-styled panaceas that inventive minds can devise.⁵⁰

These passages were quoted, in part, in the en banc decision in *Abigail Alliance*.⁵¹

So one justification for restricted access to unapproved drugs, even for the terminally ill, is paternalistic. But while the paternalistic regulation of drugs represents a compromise of autonomy, especially on the libertarian account of autonomy, it is not really a compromise of autonomy in human subjects research. For that reason, we are more concerned with the second justification for restricted access to unapproved drugs: that access must be restricted in order to maintain the clinical-trial system. In clinical trials of potentially life-saving drugs, subjects are randomly assigned to receive either standard treatment or experimental treatment (there is no placebo arm, absent unusual circumstances). The fear is that if those seeking experimental drugs have free access, they will not volunteer to be subjects in a clinical trial, where they will likely have no more than a fifty percent chance of receiving the experimental drugs they seek.

The research-based justification of restricted access is based not on the welfare of those who currently seek access to unapproved drugs, but on the welfare of the beneficiaries of research. This justification was not stressed by the court in *Abigail Alliance* in its en banc decision; the court en banc was far more concerned with the paternalistic justification.⁵² However, the potential disruption of the clinical-trial system as a result of unrestricted access was of great concern to the medical and scientific community.⁵³ This concern was not entirely speculative; in the 1980s and 1990s, the wide availability of autologous bone marrow transplant as part of a treatment for metastatic breast cancer made it difficult to enroll subjects in randomized trials of the treatment, and consequently delayed the trials. When the trials were finally completed, it was discovered that high-dose chemotherapy with bone marrow transplant was inferior to standard chemotherapy.⁵⁴

The research-based justification for limited access, along with the paternalistic justification, is inconsistent with the libertarian conception of autonomy. Referring to the research-based justification, Epstein writes that “cutting off nonparticipation alternatives that would otherwise be available smacks of a second-tier form of compulsion that should be greeted with some suspicion.”⁵⁵ Volokh assumes that

50. *Id.* at 555-56, 558.

51. *Abigail Alliance*, 495 F.3d at 713.

52. *Id.*

53. See, e.g., Emanuel, *supra* note 46, at 9.

54. *Id.* at 11-12.

55. Epstein, *The Erosion of Individual Autonomy in Medical Decisionmaking*, *supra* note 29, at 579.

the research-based justification could support some limitations on access under current constitutional doctrine, but he also expresses his distaste for that justification, and in even stronger terms: “[S]ociety would balk at a law that generally forced people to go into clinical trials, and a law that forces people to go into clinical trials if they want access to the only possibly lifesaving drugs seems to be no less coercive.”⁵⁶

While libertarians such as Volokh and Epstein have been most resistant to the research-based justification for limited access, the channeling of subjects into clinical trials may be even more questionable under the liberal conception of autonomy. The liberal conception of autonomy, far more than the libertarian one, is concerned with the way subjects are induced into volunteering for experiments. The liberal conception condemns inducements that fall far short of actual coercion.

The HHS regulations provide: “An investigator shall seek . . . consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.”⁵⁷ The phrase “undue influence” is vague, but one source of influence that has been of concern to bioethicists in the dominant liberal camp is monetary; many liberal bioethicists are concerned that subjects should not be paid too much to enter clinical trials.⁵⁸ Another indication of the kind of influence considered “undue” under the liberal conception of autonomy is 45 C.F.R. § 46.305(a)(2) of the HHS regulations, regarding the recruitment of prisoners:

Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, [must not be] of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired⁵⁹

In other words, the experience of being in a clinical trial cannot be *too attractive* to a prisoner, or his capacity to give informed consent will be considered to be impaired. Now compare these inducements, questionable under the liberal conception of autonomy, to the pressure represented by disallowing access to a drug so as to channel people into a clinical trial. Surely, the channeling pressure exerted by restrictive drug laws (possibly life-saving drug available only by participation in a clinical trial) is as great as the channeling pressure on

56. Volokh, *supra* note 30, at 1830 n.81.

57. HHS, 45 C.F.R. § 46.116 (2010); *see also* FDA, 21 C.F.R. § 50.20 (2010).

58. *See generally* COLEMAN ET AL., *supra* note 13, at 395-407.

59. 45 C.F.R. § 46.305(a)(2). There is no FDA analog.

prisoners (more attractive living conditions available only by participation in a clinical trial), at least for some patients who seek access to an experimental drug.

IRBs of course do not consider whether limited access to unapproved drugs represents an undue inducement. They take the system of drug regulation as given, and consider only inducements within that system. But if IRBs applied the same standard of undue influence to the public-policy question of whether restricted access is justified as a way of channeling people into clinical trials, they presumably would reject this justification as inconsistent with liberal autonomy.

A. Normative Evaluation

For the sake of normative analysis, it would be useful to separate the paternalistic justification for restrictive drug laws from the research-based justification. Suppose we were convinced by the paternalistic justification—convinced both that terminal patients would be better off, on average, with drug regulation and that their greater expected welfare justified this compromise of their autonomy. It would be hard, then, to evaluate the research-based justification, for we would have already accepted the policy as fully justified on another basis.⁶⁰

Fortunately, the federal rules on expanded access to unapproved drugs make it relatively easy to factor out the paternalistic justification for limited access and evaluate only the research-based justification. Section 561 of the FDCA is titled “Expanded Access to Unapproved Therapies and Diagnostics.”⁶¹ This provision authorizes the FDA to give expanded access to unapproved drugs for serious diseases, provided certain conditions are met. One of the conditions is that the FDA must determine that expanded access will not impair clinical trials.⁶² The FDA’s recently adopted final rule on expanded access contains this condition as well.⁶³

There are also paternalistic conditions in the statutory provision on expanded access and in the FDA final rule.⁶⁴ But the condition

60. By the same token, it may be hard to evaluate the paternalistic justification if we are sure we accept the research-based justification.

61. 21 U.S.C. § 360bbb (2006).

62. 21 U.S.C. § 360bbb(b)(3) (requiring that “the investigational drug or investigational device will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval”); 21 U.S.C. § 360bbb(c)(5) (requiring that “the investigational drug or investigational device will not interfere with the enrollment of patients in ongoing clinical investigations”).

63. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. 40,900 (Aug. 13, 2009) (to be codified at 21 C.F.R. pt. 312, 316). Under the final rule, the condition against impairment of clinical trials will be contained in 21 C.F.R. § 312.305(a)(3). *Id.* at 40,943.

64. See, e.g., 21 U.S.C. § 360bbb(b)(2) (requiring that the “Secretary determines that there is sufficient evidence of safety and effectiveness”); see also 21 C.F.R. § 312.305(a)(2) (2010).

that expanded access to unapproved drugs not impair clinical trials obviously contemplates situations in which the paternalistic conditions are satisfied, and the only thing standing between patients and the unapproved drugs they seek is the research-based justification for limited access to unapproved drugs.

We can therefore reformulate the issue as whether the condition against impairment of clinical trials belongs in the law. When the FDA has no paternalistic objection to access to unapproved drugs, should expanded access be provided, even if it will impair clinical trials, leading to excess deaths in the future?⁶⁵ To sharpen the case, we can assume that every patient with a given type of terminal cancer is permitted to buy an unapproved drug, *except* those who are eligible for inclusion in a clinical trial of the drug. Would this be justified? Ultimately, each observer may have his or her own intuitive response to this issue, but some arguments can be made.

Volokh and Epstein analogize the channeling of medical patients into clinical trials, through restrictive drug laws, to actual physical coercion, or to a law mandating enrollment in trials.⁶⁶ Let us consider this analogy. If there were an actual program of coerced experimentation, many people would unwillingly receive experimental medical treatment that is likely to fail. Only a small percentage of drugs entering Phase I trials are ultimately approved; for cancer drugs in the period 1991-2000, the approval rate was five percent.⁶⁷ If there were an actual program of coerced experimentation, patients would be forced to forego standard treatments of some proven effectiveness (for example, standard chemotherapy) and to receive instead an experimental treatment that is unlikely to be as safe and effective as the standard treatment.

By contrast, the channeling of patients into trials through restrictive drug laws does not subject anyone to involuntary experimental procedures. It is only patients who *want* to undergo an experimental treatment who feel any pressure from restrictive drug laws to enter clinical trials. Patients who do not want an experimental treatment experience no pressure at all to enter a clinical trial. For this reason alone, channeling through restrictive drug laws is clearly less burdensome than would be a program of actual coerced experimentation.

Another way of approaching the issue is through the moralized conception of coercion advocated by Professor Alan Wertheimer.⁶⁸

65. To set up the conflict between welfare and autonomy, we must assume not only that the clinical trial system is impaired, but that overall welfare suffers—a very reasonable assumption, we believe.

66. See *supra* note 29; Volokh, *supra* note 30.

67. Ismail Kola & John Landis, *Can the Pharmaceutical Industry Reduce Attrition Rates?*, 3 NATURE REVIEWS DRUG DISCOVERY 711, 713 (2004).

68. ALAN WERTHEIMER, COERCION (1987).

Under this approach, channeling patients into clinical trials through restrictive drug laws can be considered coercive and wrong if patients have a moral right to obtain unapproved drugs outside the context of the trials. We believe that there is a presumptive moral right to receive necessary medical treatment. This is not just a negative right against interference by the government with the private purchase of treatment, but a positive right to public provision.⁶⁹ However, experimental medical treatment cannot, as a general matter, be considered necessary medical treatment.⁷⁰ Furthermore, the basis of the presumptive moral right to necessary medical treatment, we believe, is largely or wholly welfarist; therefore, the right does not obviously apply if it would impair social welfare.

In summary, restrictive drug laws compromise autonomy, under both the liberal and libertarian conceptions of autonomy. Accepting the expert view of the FDA that restricted access to unapproved drugs is necessary to populate clinical trials, the compromise of autonomy is justified.

IV. EXCEPTIONS TO INFORMED CONSENT REQUIREMENTS: EMERGENCY RESEARCH AND MINIMAL-RISK RESEARCH

People who are “channeled” into a clinical trial still go through an informed-consent procedure. Sometimes, however, the federal regulations governing human subjects research permit experiments with no consent at all, through exceptions to the requirement of informed consent. Two regulatory exceptions in particular appear to compromise autonomy: those for emergency-care research and minimal-risk research. After describing these exceptions and providing a guarded welfarist endorsement of each, we will consider whether they do in fact compromise autonomy.

A. *Emergency Care Research*

Under both the HHS regulations and the FDA regulations, IRBs may waive the requirement of informed consent for emergency-care research, provided certain conditions are met. Among these conditions are that the research subjects are in a “life-threatening situation” and consequently unable to give informed consent; “available treatments are unproven or unsatisfactory”; there is no time to obtain consent from legally authorized representatives; participation in the research “holds out the prospect of direct benefit to the subjects” (i.e., it is therapeutic research); and there has been consultation

69. See Mark S. Stein, *Necessity, Not Autonomy*, 86 TEX. L. REV. 15 (2007), available at <http://www.texaslrev.com/sites/default/files/seealso/vol86/pdf/86TexasLRevSeeAlso15.pdf>.

70. See *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695, 708 (D.C. Cir. 2007).

“with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn.”⁷¹ The emergency exception was added to the regulations in 1996.⁷²

The welfarist case for an emergency-research exception is very strong. Some medical innovations must be tested, if at all, only on patients who are unable to give informed consent or even substituted consent. If there can be no testing without consent, great advances may be lost. The problem is particularly severe if the innovation is a new drug. In that case, the new product cannot be used unless it is tested in human trials; if it cannot be tested, it will never be used. The problem is not quite so severe with new surgical techniques and other innovations that do not require FDA approval.

Successful trials of thrombolytic (clot-dissolving) drugs for heart attack, conducted in the 1980s, provide some indication of how important an emergency exception can be. As related by Collins, Doll, and Peto, a large trial was conducted both in Britain and in the United States. In Britain, informed-consent requirements were flexible, but in the United States, the trial protocol required that doctors present a lengthy consent form to the patients (there was as yet no emergency exception).⁷³ Collins, Doll, and Peto suggest that because of what they call the “inhumane US consent procedure,”⁷⁴ recruitment into the trial was much slower in the United States than in Britain, delaying the end of the trial by six months. They estimate that as the trial results “have transformed medical practice” worldwide, the delay in United States recruitment resulted in “about 10,000 unnecessary deaths.”⁷⁵ This may be an exaggerated estimate, but the most chilling aspect of the tale is that if there were no emergency research exception, a similarly valuable innovation today might not be tested at all.⁷⁶

Experience under the emergency-research exception, unfortunately, has not been all one could have hoped. Several of the early trials conducted under the waiver were for blood substitutes, which

71. 21 C.F.R. § 50.24 (2010) (FDA waiver); 61 Fed. Reg. 51,531 (Oct. 21, 1996) (codified at 45 C.F.R. pt. 46) (HHS waiver). The HHS exception is not in the regulation itself; it was announced in the Federal Register, under authority of 45 C.F.R. § 46.101(i).

72. Protection of Human Subjects; Informed Consent, 61 Fed. Reg. 51498 (Oct. 2, 1996) (codified at 21 C.F.R. pts. 50, 56, 312, 314, 601, 812, 814).

73. Rory Collins, Richard Doll, & Richard Peto, *Ethics of Clinical Trials*, in INTRODUCING NEW TREATMENTS FOR CANCER 54-55 (1992).

74. *Id.* at 55.

75. *Id.*

76. Ironically, while a trial of drugs to treat heart attack would now presumably be eligible for a waiver of informed-consent requirements in the United States, those requirements have become stricter in the European Union, and emergency-care research has become more difficult. See Malcolm G. Booth, *Informed Consent in Emergency Research: A Contradiction in Terms*, 13 SCI. & ENGINEERING ETHICS 351 (2007).

were administered to trauma victims without consent. The blood substitute trials led to excess deaths; according to one meta-analysis, use of a blood substitute increased the risk of death by thirty percent.⁷⁷ These unfortunate results should remind us that the requirement of informed consent does have considerable instrumental value in preventing harm to subjects.⁷⁸

B. *Minimal-Risk Research*

The HHS regulations, but not the FDA regulations, also permit IRBs to waive or alter informed consent requirements if “[t]he research involves no more than minimal risk to the subjects,” and if additional conditions are met, including that the research “could not practicably be carried out without the waiver.”⁷⁹ Minimal risk is defined, in Subpart A of the HHS regulations, as meaning that “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”⁸⁰

The minimal-risk exception is commonly used to obtain authorization for deceptive psychological experiments. As deception is a necessary part of these experiments, they cannot “practicably” be done if the subjects are given full information. Another use for the minimal-risk exception, which has aroused some controversy, is to authorize unconsented-to research on identified medical records or identified

77. See Charles Natanson et al., *Cell-Free Hemoglobin-Based Blood Substitutes and Risk of Myocardial Infarction and Death: A Meta-Analysis*, 299 JAMA 2304, 2306 (2008).

78. Though there was also a blood substitute trial of consenting orthopedic patients, conducted in Sweden. Christina Olofsson et al., *A Multicenter Clinical Study of the Safety and Activity of Maleimide-Polyethylene Glycol-Modified Hemoglobin (Hemospan) in Patients Undergoing Major Orthopedic Surgery*, 105 ANESTHESIOLOGY 1153 (2006).

79. 45 C.F.R. § 46.116(d) (2010). In its entirety, the exception reads as follows:

An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

- (1) The research involves no more than minimal risk to the subjects;
- (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- (3) The research could not practicably be carried out without the waiver or alteration; and
- (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Id.

80. 45 C.F.R. § 46.102(i). There are some uncertainties and disputes about the meaning of this definition. See COLEMAN ET AL., *supra* note 13, at 280-81. Also, there is a somewhat different definition of “minimal risk” in Subpart C, governing research on prisoners: “Minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.” 45 C.F.R. § 46.303(d) (emphasis added).

stored tissue samples.⁸¹ Such research may present no more than minimal risk if the risk of a damaging disclosure of private information is sufficiently low.⁸² However, there is disagreement over the “impracticable” requirement: if it would be costly and time-consuming to seek consent for the analysis of identified stored tissue samples, does that make it “impracticable”?⁸³

The minimal-risk exception seems generally justified based on welfarist considerations. The less risk of harm an experiment poses, the less need there is for informed consent as a means to prevent that harm.

C. Do the Emergency and Minimal-Risk Exceptions Compromise Autonomy?

If the principle of informed consent means that it is forbidden to experiment on people without their informed consent (or the informed consent of their legal representatives), then obviously the emergency-research exception and the minimal-risk exception violate the principle of informed consent. And if this interpretation of informed consent expresses the meaning of autonomy, then these exceptions compromise autonomy.

The emergency-research exception is indeed generally seen as compromising autonomy for the sake of the welfare of research beneficiaries. Baruch Brody, for example, writes that the FDA’s emergency regulations could not be justified if informed consent were seen as an absolute value: “[T]he FDA regulations represent the triumph of pluralistic casuistry over the absolutism of single values. To my mind, this is a welcome development in research ethics.”⁸⁴ Jay Katz, a leading advocate of informed consent, has reservations about aspects of the emergency exception, but he agrees that some exception is justified in the emergency context, and he further agrees that such an exception compromises autonomy:

While the principle of self-determination in the conduct of human experimentation should not lightly be set aside, I have always believed that principles must have exceptions as long as they are rigorously justified and most narrowly drawn. A waiver of informed

81. If records or tissue samples are not identifiable, or if the researcher does not record identifiable information, the regulations do not require researchers to obtain informed consent. 45 C.F.R. §§ 46.102(f)(2), 46.101(b)(4).

82. There is a parallel exception under the HIPAA regulations. 45 C.F.R. § 164.512.

83. See COLEMAN ET AL., *supra* note 13, at 719.

84. Baruch A. Brody, *New Perspectives on Emergency Room Research*, HASTINGS CENTER REP, Jan.-Feb. 1997, at 7, 9.

consent in the situations encompassed by the regulations can be justified and my reservations are not that a waiver was granted.⁸⁵

The minimal-risk exception arguably represents an even greater compromise of autonomy than the emergency-research exception. Under the minimal-risk exception, consent can be waived or altered by the IRB if it would be “impracticable” to obtain full informed consent, even though subjects are actually able to consent. From the standpoint of autonomy, it may be worse to waive consent when the subject can consent (but seeking consent would be impracticable) than when the subject cannot consent at all.

Probably the only way to deny that the two exceptions compromise autonomy for the sake of welfare is to adopt a theory of hypothetical consent as satisfying the dictates of autonomy.⁸⁶ Professor Russell Korobkin has advocated this theory in connection with the minimal-risk exception and research on stored tissue samples;⁸⁷ it could also be used to justify some applications of the emergency-research exception.

Suppose that a person cannot consent to be a subject, or that the experiment will not be done if consent must be sought. Under the hypothetical-consent view, the question becomes whether the prospective subject *would* have consented if, counterfactually, the person had been able to give fully informed consent. If there is hypothetical consent—if the person would have consented to be a subject had the person been able to do so—there is no violation of autonomy. Indeed, it could be argued, under the hypothetical-consent view, that if a person would have consented to be a subject, it is a violation of autonomy *not* to include that person as a subject. Korobkin advances this argument in rejecting a rule that would always require researchers to obtain consent before doing stem-cell research on stored tissue samples; that rule, he claims, “would protect the autonomy of those who would have declined to participate, but it would undermine the autonomy of those who would have agreed to participate but are effectively prohibited from making that choice.”⁸⁸

What if our best judgment is that some prospective subjects would have consented and some would have refused? On stored tissue samples, Korobkin believes that we should follow a hypothetical majoritarian approach, effecting “what would have been the autonomous

85. Jay Katz, *Blurring the Lines: Research, Therapy, and IRBs*, HASTINGS CENTER REP, Jan.-Feb. 1997, at 7, 9.

86. As to one application of the minimal-risk exception—regarding stored tissue samples and medical records—it may be possible to deny that there is an autonomy interest at all. We do not pursue this possibility here.

87. RUSSELL KOROBKIN WITH STEPHEN R. MUNZER, STEM CELL CENTURY 168-69 (2007); Russell Korobkin, *Autonomy and Informed Consent in Nontherapeutic Biomedical Research*, 54 UCLA L. REV. 605, 624-25 (2007).

88. Korobkin, *supra* note 87, at 624 (referring to guidelines of the National Research Council).

choice of most tissue providers.”⁸⁹ Strikingly, a hypothetical majoritarian approach gives no greater weight to the unwillingness of some people to be subjects than to the altruistic willingness of others to be subjects; it does not make abstention from experimentation the default position.⁹⁰

With respect to research activities that may be eligible for the minimal-risk exception, the hypothetical-consent view implies that two counterfactual requirements must be satisfied. It is necessary, of course, that most of the subjects would have given informed consent. But in addition, informed consent can only be waived if requiring informed consent would have prevented the research from being conducted. If it would be difficult and expensive for researchers to seek informed consent, but they would still do so if required, then they must do so; in that situation, it is possible to give effect to the actual autonomous choices of all prospective subjects, both those who consent to be a subject and those who decline. In principle, then, the hypothetical-consent view suggests that high-value research should be less eligible for a waiver of consent than low-value research, as researchers will more likely be willing to seek consent for high-value research.

In considering the possible application of the hypothetical-consent view to emergency research, it is useful to compare the emergency exception to informed consent in research, contained in the federal regulations, with the common-law emergency exception to informed consent in the treatment setting. The justification for the emergency-treatment exception is often expressed in hypothetical, counterfactual terms: “[S]ince reasonable persons would consent to treatment in an emergency if they were able to do so, it is presumed that any particular patient would consent under the same circumstances.”⁹¹ Such explanations of the emergency-treatment exception might be taken to suggest that the emergency-research exception can also be justified based on a hypothetical-consent approach. However, emergency treatment without consent benefits the patient. We cannot say the same of emergency experimentation without consent. Indeed, the emergency-treatment exception is strictly limited to necessary procedures; it does not extend even to beneficial actions that are not necessary, much less to procedures that are primarily designed to benefit those other than the patient.⁹² In short, if the emergency-research

89. *Id.*

90. What if the majoritarian approach were applied to a situation of actual consent rather than hypothetical consent? Suppose that researchers proposed to experiment on a group of people that for some reason could not be separated. A majority of the group consented, but a minority objected. Would it be more consistent with autonomy to experiment on the unwilling minority than to abstain from experimenting on the willing majority? This is not a rhetorical question.

91. BERG ET AL., *supra* note 33, at 76.

92. *Id.* at 77-78.

exception were tested under the standard used for the emergency-treatment exception, the emergency-research exception would almost always fail.

What, then, should we make of the view that exceptions to informed consent do not compromise autonomy if there is hypothetical consent? The hypothetical-consent view is pretty clearly inconsistent with the dominant liberal conception of autonomy. The liberal conception has a strong default position against experimentation, as evidenced by its preoccupation with informed consent. Beauchamp and Childress explicitly reject the hypothetical-consent view: "Consent should refer to an individual's actual choices, not to presumptions about the choices the individual would or should make."⁹³

Hypothetical consent can perhaps more easily be integrated into the libertarian conception of autonomy. The libertarian conception of autonomy does not have so strong a default position against experimentation, in the sense of requiring far more informed consent to participate in an experiment than not to participate. As noted, libertarians tend not to see the decision to enter an experiment as being a special decision, subject to special rules. On the other hand, many who hold the libertarian conception of autonomy would likely see experimentation without consent, for emergency research or minimal-risk research, as a coerced exchange necessitating compensation.⁹⁴ Many libertarians would likely be skeptical of the idea that hypothetical consent can excuse compensation.

In our opinion, the emergency-research exception and the minimal-risk exception do compromise autonomy for the sake of nonsubject welfare. The hypothetical-consent approach cannot reconcile these exceptions to autonomy under the dominant liberal conception of autonomy, and hypothetical consent is questionable even under the libertarian conception of autonomy. It also bears repeating that some applications of the two exceptions could not be justified even under a hypothetical-consent approach.

While the two exceptions compromise autonomy, they are nevertheless probably justified on welfarist grounds. They only lack justification if they are self-defeating, if they do not actually result in greater welfare.

93. BEAUCHAMP & CHILDRESS, *supra* note 33. They add that there can be implied consent based on choices actually made.

94. With respect to minimal-risk research, this assumes that there is a libertarian right against the kind of activity or interaction constituting the experiment. Libertarians probably do not recognize a generalized right not to be the subject of an experiment: there are rights to bodily integrity, to property, etc., and researchers need obtain consent only if they would violate one of these rights.

V. OFFER OF TREATMENT ON CONDITION THAT SUBJECTS WAIVE INFORMED CONSENT

The exceptions to informed consent discussed above are at the periphery of human subjects research. In this Part, we argue that the blind clinical trial,⁹⁵ which is at the core of human subjects research, inherently involves a compromise of autonomy. In the blind clinical trial, subjects are offered medical treatment on the condition that they give up (1) the right to know what treatment they are receiving, and (2) the right to participate in decisionmaking about their treatment. Such an offer of treatment conditioned on a waiver of treatment-related informed-consent rights does not contravene the libertarian conception of autonomy, but it does contravene the dominant liberal conception of autonomy.

We emphasize that we do not consider the blind clinical trial to be unethical. It is ethical, even though it inherently compromises liberal autonomy, because it serves social welfare.

In order to clarify issues of autonomy and required waiver, let us first suppose that researchers offered subjects participation in a clinical trial in exchange for the waiver of informed-consent rights that are contained in the regulations governing human subjects research. For example, the regulations require disclosure of “any reasonably foreseeable risks or discomforts to the subject.”⁹⁶ Suppose that clinical researchers offered subjects enrollment in a clinical trial on the condition that the subjects give up any right to know of foreseeable risks and discomforts. In a study governed by the regulations, that would be a violation of the regulations. There are a small number of clinical studies that are not governed by either the HHS or FDA regulations; in those studies, an offer of enrollment in a trial conditioned on a waiver of information about risks would not violate the regulations. But the question, in either case, is whether such an offer would constitute a compromise of autonomy.

From a libertarian perspective, an offer of enrollment in a trial conditioned on a waiver of information about risks probably would not constitute a compromise of autonomy. The researchers are offering potential subjects a “capitalist act[] between consenting adults,” to quote Robert Nozick.⁹⁷ The researchers are truthfully and un-fraudulently explaining the information that potential subjects must agree to forego if they are to be accepted into the study: any information about risks. From a libertarian perspective, a subject who ac-

95. Most clinical trials are blind (or double-blind or triple-blind); the subjects are not told what treatment they are receiving, lest that knowledge affect their perception of the effectiveness of the treatment.

96. HHS, 45 C.F.R. § 46.116(a)(2) (2010); FDA, 21 C.F.R. § 50.25(a)(2) (2010).

97. NOZICK, *supra* note 27, at 163.

cepts such an offer has not experienced a compromise of autonomy; the subject has exercised his autonomy.⁹⁸

The libertarian analysis of this hypothetical offer of enrollment conditioned on a waiver of information about risks demonstrates the point we made in the Introduction that informed consent (as opposed to simply consent) is a liberal principle, not a libertarian principle. Under the dominant liberal conception of autonomy, it should be clear, the hypothetical offer of inclusion conditioned on waiver of knowledge about risks *would* compromise autonomy. Informed consent should be respected and promoted, under the liberal view, and an attempt to contract around the requirements of informed consent compromises informed consent and autonomy.

This conclusion does not, in itself, validate our argument that the blind clinical trial inherently compromises autonomy. As indicated, the blind clinical trial involves the required waiver of the right of medical patients to know what treatment they are receiving and to participate in decisionmaking about their treatment. The analysis just offered does not apply to the required waiver of these rights, because they are not rights guaranteed by the ethics and regulations governing clinical research. These rights are, however, guaranteed by the ethics and regulations governing medical *treatment*. As we will show, participation in blind clinical research entails the required waiver of treatment-related informed consent rights.⁹⁹ For that reason, the blind clinical trial inherently involves a compromise of liberal autonomy.

98. It might superficially seem that libertarian acceptance of required waiver here is inconsistent with libertarian opposition to channeling patients into clinical trials, discussed in Part III. As to channeling, libertarians say it's wrong to impose a condition on obtaining medical treatment (enrollment in a trial in order to get an experimental drug); here, libertarians say it's acceptable to impose a condition (waiver of informed-consent rights in order to enroll in a trial). But libertarians only oppose "channeling" because the condition is imposed by the government, which prohibits a private bargain between drug companies and patients. If the condition were imposed by the drug companies themselves, libertarians would not object.

99. One of the few observers to understand that informed consent to participate in blind clinical research entails a kind of waiver of informed consent to treatment is Professor Mark Hall. He writes:

Waiver of informed consent is commonly practiced in even the most ethically scrutinized treatment settings—medical research. Despite the rigorous application of informed consent principles that is necessary to meet federal funding requirements, research subjects routinely are allowed to waive full disclosure in the interests of science when they participate in double-blind studies

Mark A. Hall, *A Theory of Economic Informed Consent*, 31 GA. L. REV. 511, 567 (1997). While Hall agrees with us that the blind clinical trial involves a waiver of informed consent, he draws a different conclusion from this understanding. Hall argues that since waiver of informed consent is accepted in clinical research, it should also be accepted in clinical practice, as a cost-saving measure. *Id.*

For purposes of our argument, we will speak only of clinical trials in which all subjects receive medical treatment: active-controlled trials rather than placebo-controlled trials. We believe our argument applies also to placebo-controlled trials, but we leave them aside to forestall objections. We will proceed by asking first, whether a required waiver of treatment-related informed-consent rights such as is inherent in the blind clinical trial would be considered a compromise of autonomy in the nonresearch context. Then we will consider whether the fact that medical treatment is given in the research context changes the analysis.

The principle of informed consent operates in the treatment setting as well as in the research setting. In the treatment setting, informed consent is thought to have two components: the right to be informed and the right to decide.¹⁰⁰ It is well established that the right to information includes the right to know what procedures will be used.¹⁰¹

Suppose that a doctor agreed to treat a patient only on condition that the doctor alone would make all treatment decisions, with no input from the patient, and that the doctor would not even tell the patient what treatment the doctor was administering. In other words, the doctor offers treatment on condition that the patient waive her right to informed consent.¹⁰² Granted, this hypothetical offer of treatment involves a more extensive required waiver than the blind clinical trial. Here, the clinical practitioner is not merely demanding the waiver of *some* informed-consent rights; he is demanding the waiver of all informed-consent rights. One could make the example more analogous by supposing that the doctor tells the patient he will insist on choosing randomly between two possible treatments, and he will refuse to inform the patient which treatment is chosen.¹⁰³

In any event, would such an offer of medical treatment conditioned on the waiver of informed-consent rights be a compromise of

100. BERG ET AL., *supra* note 33, at 88-89.

101. *Id.* at 54-55 ("Almost all courts and statutes require that the physician provide the patient with an explanation of the nature of the procedure or treatment, that is, what is going to happen."). Actually, the regulations, by their terms, also require "a description of the procedures to be followed, and identification of any procedures which are experimental." HHS, 45 C.F.R. § 46.116(a)(1); FDA, 21 C.F.R. § 50.25(a)(1). If strictly interpreted, this rule would prohibit the blind clinical trial, but it is (sensibly) interpreted to require only a description of the procedures that *might* be followed in a randomized experiment.

102. Why would the doctor insist on such a waiver of informed-consent rights, assuming there is no research involved? Perhaps he sees the obligations placed on him by the informed-consent doctrine as pointlessly burdensome.

103. In this modified example, however, it's hard to come up with a motivation for the doctor's behavior that is not utterly frivolous. Perhaps the doctor wants some unpredictability in his life (hence the random assignment), and he also wants some mystery (hence the nondisclosure).

autonomy in the nonresearch setting? Once again, the offer would not compromise autonomy under the libertarian conception of autonomy. Libertarians resist limitations on freedom of contract; they tend to believe that all rights can be waived. Richard Epstein and other libertarian bioethicists oppose the rule against waivers of liability for medical malpractice.¹⁰⁴ Robert Nozick even argued that one should be able to sell oneself into slavery.¹⁰⁵

But under the dominant liberal conception of autonomy, informed consent is not merely a default rule supplied by the state, subject to change; it is a value that doctors are supposed to respect. As stated in the AMA's Code of Medical Ethics:

The patient's right of self-decision can be effectively exercised only if the patient possesses enough information to enable an informed choice. The patient should make his or her own determination about treatment. The physician's obligation is to present the medical facts accurately to the patient or to the individual responsible for the patient's care and to make recommendations for management in accordance with good medical practice.¹⁰⁶

Required waiver of informed-consent rights would of course violate this provision of the AMA Code of Ethics.

It is true that the right to informed consent in the treatment context can be waived at the volition of the *patient*, unlike a medical-malpractice claim of negligent injury.¹⁰⁷ But the paradigmatic waiver situation is one in which the doctor begins telling the patient about the risks of treatment, and the patient says, "Stop, I don't want to hear any more." Or the doctor begins explaining to the patient that two or more courses of treatment are available, and the patient says, "You decide." In such cases, the patient has the opportunity to receive information and/or participate in decisions, but declines to take advantage of the opportunity. By contrast, the offer of medical treatment conditioned on a waiver of informed consent seeks to deprive the patient of these opportunities at the beginning.

For the doctor to demand waiver of informed consent as a condition of treatment is at least arguably inconsistent with some of the court decisions establishing the doctrine of informed consent in the treatment context.¹⁰⁸ Physician-demanded waiver is also arguably

104. Epstein, *Contractual Principle Versus Legislative Fixes*, *supra* note 29, at 505-11. The leading case on the unenforceability of prior waivers of medical malpractice liability is *Tunkl v. Regents of Univ. of Cal.*, 383 P.2d 441, 446-47 (Cal. 1963).

105. NOZICK, *supra* note 27, at 331.

106. AMERICAN MEDICAL ASSOCIATION, CODE OF MEDICAL ETHICS, OPINION 8.08 (2010) available at <http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion808.shtml>.

107. BERG ET AL., *supra* note 33, at 85-90.

108. *Henderson v. Milobsky*, 595 F.2d 654, 656 n.8 (D.C. Cir. 1978) ("[P]hysicians and courts alike must accept the patient's election to know nothing and instead to rely com-

inconsistent with at least some state statutes codifying the doctrine of informed consent.¹⁰⁹ And the mere fact that a waiver is valid if initiated by the patient does not necessarily mean that it is valid if demanded by the doctor. Patients may validly waive their right of privacy under the HIPAA regulations, but the regulations state that in general, “[a] covered entity may not condition the provision to an individual of treatment, payment, enrollment in the health plan, or eligibility for benefits on the provision of an authorization.”¹¹⁰

Regardless of whether the practice would be illegal,¹¹¹ it seems clear that in the nonresearch context, offering medical treatment on condition that the patient waives her right to informed consent would be a compromise of liberal autonomy. Does it make a difference when the treatment is given in the research context? Our position is that it makes a difference in the bottom-line ethical evaluation of the practice, but that moving from the nonresearch context to the research

pletely upon the physician The keystone, however, is that it is the patient, not the physician or the medical profession, who defines the scope of the pre-decision opportunity to know.”); *Cobbs v. Grant*, 502 P.2d 1, 12 (Cal. 1972) (“[A] medical doctor need not make disclosure of risks when the patient requests that he not be so informed.”).

109. The New York informed consent statute provides:

It shall be a defense to any action for medical, dental or podiatric malpractice based upon an alleged failure to obtain such an informed consent that... the patient assured the medical, dental or podiatric practitioner that he did not want to be informed of the matters to which he would be entitled to be informed

N.Y. Pub. Health Law § 2805-d(4) (McKinney 2010).

110. 45 C.F.R. § 164.508(b)(4) (2010). There are exceptions to this general rule. One is that a provider of care in the context of clinical research may condition treatment on receipt of an authorization. *Id.*

111. Recognition that informed consent to research entails a waiver of informed consent to treatment raises perhaps the tiniest of legal clouds over the blind clinical trial. The HHS regulations contain an antipreemption provision. 45 C.F.R. § 46.101(f). So if state-law doctrines of informed consent prohibit the offering of medical treatment on condition that the patient waives informed-consent rights, the blind clinical trial may be a violation of state law, which arguably is not preempted by the regulations. Furthermore, the HHS and FDA regulations make it a condition of IRB approval of research that

[n]o informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject’s legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

HHS, 45 C.F.R. § 46.116; *see also* FDA, 21 C.F.R. § 50.20 (2010). The main purpose of this provision is clearly to preclude a waiver of negligence liability for personal injuries. That does not, however, make the provision inapplicable to the required waiver of informed consent, especially since the doctrine of informed consent, in the treatment context, is considered part of the doctrine of negligence. *See* BERG ET AL., *supra* note 33, at 134-36. By waiving her right to information about treatment, and to determine the course of her treatment, a subject could be considered to have waived a right to be free of negligence.

Of course, we do not think for a moment that the blind clinical trial will be held to be illegal. Even if the legal analysis just offered were given any credence, some way would be found to uphold the blind clinical trial, because of its great social utility—and properly so.

context does not change the analytical conclusion that liberal autonomy is compromised.

There has been an extensive debate over whether and how the ethics of medical treatment differs from the ethics of medical research (including research that involves medical treatment).¹¹² Superficially, our argument that the blind clinical trial entails a waiver of treatment-related rights might seem to commit us to the position that there is no difference between the ethics of treatment and the ethics of research. In fact, we take the opposite position. To avoid confusion, then, it may be best to distinguish between different reactions our argument might provoke.

Some might accept our claim that required waiver of treatment-related rights compromises liberal autonomy. They might say that just as required waiver in the non-research context would be unethical, so also the blind clinical trial is unethical, as it compromises autonomy. They might conclude that the blind clinical trial should be abolished.

We, of course, disagree. We believe that required waiver would be at least presumptively unethical in the nonresearch context, but we draw a different conclusion in the research context. The blind clinical trial is ethical, even though it compromises liberal autonomy, because it serves social welfare.

A more likely objection to our argument is that required waiver of treatment-related rights does not compromise autonomy in the research context, even though it would compromise autonomy in the nonresearch context (and would probably be unethical in that context). Here, there is no disagreement over the bottom-line ethical conclusion: Both we and our objectors would apply a different ethical standard to required waiver in the research context than in the non-research context. The disagreement is whether required waiver of treatment-related rights in clinical research (1) compromises autonomy, but is nevertheless ethical (our position), or (2) does not compromise autonomy at all.

Patients in the nonresearch context have an autonomy interest in knowing what treatment they are receiving, and in participating in the treatment decision. What happens to this autonomy interest when the treatment is provided as part of a medical experiment? In

112. See, e.g., Carl H. Coleman, *Duties to Subjects in Clinical Research*, 58 VAND. L. REV. 387 (2005); E. Haavi Morreim, *The Clinical Investigator as Fiduciary: Discarding a Misguided Idea*, 33 J.L. MED. & ETHICS 586 (2005); Kathleen Cranley Glass & Duff Waring, *The Physician/Investigator's Obligation to Patients Participating in Research: The Case of Placebo Controlled Trials*, 33 J.L. MED. & ETHICS 575 (2005); Franklin G. Miller & Howard Brody, *A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials*, 33 HASTINGS CENTER REPORT 19 (2003).

our view, it makes more sense to say that the autonomy interest is overridden by social welfare than to say that it simply disappears.

A third possible reaction to our argument is that required waiver of treatment-related rights does not compromise autonomy either in the research context or in the nonresearch context. This is a libertarian position. It is not really opposed to our argument, because we only claim that the blind clinical trial compromises liberal autonomy, not libertarian autonomy. If you are a libertarian, you can support the blind clinical trial without conceding that it involves any compromise of autonomy (at least with respect to the required waiver of rights). If you are a liberal who supports the blind clinical trial, you should concede that it involves some compromise of autonomy.

VI. SELECTION OF SUBJECTS

The value of autonomy, at least on the liberal view, is more concerned with preventing people from being *included* in experiments against their will than with preventing people from being *excluded* from experiments against their will. Nevertheless, laws that exclude people from being subjects also raise autonomy issues. Under HHS regulations an IRB cannot approve research unless it determines that the “[r]isks to subjects are reasonable in relation to the anticipated benefits” of the research to subjects and others.¹¹³ If the risks are too high, the research cannot proceed, even if the subjects would have given fully informed consent. This limitation reflects a welfarist paternalism. Does the paternalism of 45 C.F.R. § 46.111(a)(2), in itself, represent a compromise of autonomy?

In the situation where an entire study has been scrapped as too risky, the compromise of autonomy seems somewhat attenuated. There are no individuals who seek to enter the study, because the study does not occur. If an experiment does not take place because the IRB deems it too risky, whose autonomy is compromised? It may be possible to say that autonomy in the abstract is compromised; that position seems plausible to us. It is also plausible to say, in such a case, that the regulations, as enforced by the IRB, have limited the autonomy of the researchers, who have been barred from their chosen course. However, we are interested here in the autonomy of the subjects or potential subjects.

The possible compromise of autonomy is sharper when particular individuals are prevented from becoming subjects because it is deemed, as to them, that the risks would not be reasonable in relation to the benefits. So we can ask again: If someone would like to be

113. HHS, 45 C.F.R. § 46.111(a)(2); FDA, 21 C.F.R. § 56.111(a)(2).

a subject, but is excluded because the experiment would be too risky for him, has the person's autonomy been compromised?

Under the libertarian conception of autonomy, it seems the answer must be yes. To libertarians, paternalistic limitations on choice are inherently violative of autonomy.¹¹⁴ Under the dominant liberal conception, the situation is somewhat more complicated. Barring someone from being a subject *could* be a compromise of autonomy under the liberal conception. The prospective subject might have made a completely informed, voluntary and authentic decision to participate, even though the experiment poses particular risks to him that are, under the regulations, unreasonable.¹¹⁵ The advocate of liberal autonomy could point to imperfections in real-world informed-consent procedures as a justification for the exclusion of high-risk subjects from trials; maybe the volunteers would not fully comprehend the risks, despite procedures that seek to guarantee informed consent.¹¹⁶ But at some point, we think, even the advocate of liberal autonomy would have to agree that a welfarist-paternalist limitation on who can be a subject means that autonomy is being compromised for the sake of another value, namely, welfare.

A. *Gelsinger Case*

In short, the paternalism of the regulations, with respect to the selection of subjects, represents a compromise of autonomy both on the libertarian view and on the liberal view of autonomy. However, the regulations do not go far enough in establishing a welfarist criterion for the selection of subjects. This is one conclusion that can be drawn from the tragic Gelsinger case, in which a relatively healthy subject died after researchers were persuaded not to test a gene-therapy treatment on terminal babies, but instead to test it on adults with a mild form of the genetic disease. This case has previously been addressed by one of the authors;¹¹⁷ we now add legal analysis.

114. This is leaving aside the complicating factor that under the HHS regulations, the restrictions may be tied to funding. A libertarian might object to government funding of medical research, but once that hurdle is passed, contractual restrictions tied to the funding might be seen as legitimate. Suppose, for example, that a private philanthropic organization funded research, but only on condition that studies met a risk/benefit criterion. This would be paternalism, but paternalism by a private actor not written into law. The conditions that a private philanthropist attached to the funding of research presumably would not be considered a violation of libertarian autonomy.

115. We assume that the IRB correctly interprets the regulations.

116. Why couldn't this argument be made under the libertarian conception? It is not completely plausible even under liberal conception, and under the libertarian conception it would be two steps removed from the legitimate concerns of libertarianism; remember that informed consent itself can only be justified, under the libertarian conception, as prophylactic of actual deception.

117. Julian Savulescu, *Harm, Ethics Committees and the Gene Therapy Death*, 27 J. MED. ETHICS 148 (2001). For a similar view, see JONATHAN BARON, *AGAINST BIOETHICS* 1-3 (2006).

Jesse Gelsinger had a relatively mild form of ornithine transcarbamylase (OTC) deficiency, a rare metabolic disorder in which the liver is unable to process ammonia. In 1999, at the age of eighteen, he enrolled as a subject in a Phase I gene-therapy trial for the treatment of OTC deficiency. The gene-therapy trial was conducted by researchers at the University of Pennsylvania's Institute for Human Gene Therapy (Penn IHGT). On September 13, 1999, the researchers injected Gelsinger with a weakened cold virus (adenovirus) carrying corrective OTC genes. Four days later, he was dead from what was probably an immune reaction to the virus vector. This was the first death directly attributed to gene therapy.¹¹⁸

The gene therapy treatment that researchers tested on Gelsinger was not designed to treat people who, like Gelsinger, had a relatively mild form of OTC deficiency. The treatment was intended for neonates with the more severe and usually fatal form of the disease. The researchers had originally planned to test the treatment on terminal neonates. But they were persuaded by Art Caplan, a famed bioethicist at the University of Pennsylvania, to test the treatment instead on adults—men with a relatively mild version of the disease or female carriers of the disease. In an interview with the *New York Times* after Gelsinger's death, Caplan justified his intervention by saying that parents of dying infants are incapable of giving informed consent: "They are coerced by the disease of their child."¹¹⁹

Penn IHGT's protocol for the OTC gene therapy trial had been reviewed by the FDA and by the Recombinant DNA Advisory Committee (RAC) of the NIH.¹²⁰ There was substantial opposition to the trial in the RAC because monkeys had died after being given a similar (but much stronger) treatment, and because of the potential for lethal liver inflammation.¹²¹ The RAC ultimately approved the trial, with one member dissenting, after Penn IHGT agreed to deliver the virus vector intravenously rather than directly into the liver.¹²² The FDA, however, was concerned about the infection of reproductive cells (germline modification) from this mode of delivery, and it made Penn IHGT go back to direct liver injection.¹²³

118. See Sheryl Gay Stolberg, *The Biotech Death of Jesse Gelsinger*, N. Y. TIMES, Nov. 28, 1999, § 6, at 137 [hereinafter Stolberg, *Biotech Death*]; Sheryl Gay Stolberg, *F.D.A. Officials Fault Penn Team in Gene Therapy Death*, N. Y. TIMES, Dec. 9, 1999, § A, at 22; Rick Weiss & Deborah Nelson, *FDA Halts Experiments On Genes at University; Probe of Teen's Death Uncovers Deficiencies*, WASH. POST, Jan. 22, 2000, § A, at 1.

119. Stolberg, *Biotech Death*, *supra* note 118 (internal quotation marks and citation omitted).

120. *Id.*

121. *Id.*

122. *Id.*

123. *Id.*

After Gelsinger's death, there were investigations by the FDA, the University of Pennsylvania, and a Senate subcommittee.¹²⁴ The FDA suspended gene-therapy trials by Penn IHGT, and the University of Pennsylvania subsequently limited it to animal studies.¹²⁵ Gelsinger's family also filed a lawsuit against various individuals and institutions associated with the trial.¹²⁶ The suit was settled on undisclosed terms.¹²⁷

A major focus of the investigations and the lawsuit was deficiencies in the informed-consent process. The FDA determined that Penn IHGT improperly failed to disclose to Gelsinger that other, previously-treated subjects in the study had suffered serious side effects and that monkeys had died in animal studies.¹²⁸ Attempting to draw lessons from Gelsinger's death, Theodore Friedmann, director of the Program in Human Gene Therapy at the University of California at San Diego, stated:

The single most important mechanism for ensuring patient protection from inherent risks of clinical experiments, unrealistic expectations, and potential conflicts of interest of the investigator is accurate and full disclosure of potential risks and benefits and a well-executed informed consent process.¹²⁹

Informed consent does play an important (welfarist) role in protecting subjects from harm, as suggested previously. It is not clear, however, that even a perfect informed-consent process would have saved Gelsinger's life. Gelsinger's motivation was highly altruistic. Before he entered the experiment, he reportedly told a friend: "What's the worst that can happen to me? . . . I die, and it's for the babies."¹³⁰

Another finding by the FDA was that Gelsinger should not have been allowed to participate in the study because he had too much ammonia in his blood at the time he was given the experimental treatment.¹³¹ Once again, however, it is not clear whether Gelsinger's ammonia level contributed to his death. In its February 14, 2000 response to FDA action, Penn IHGT stressed that "available scientific evidence does not establish *any* causal link between Jesse Gelsinger's

124. *Id.*

125. *Id.*

126. *Id.*

127. *Id.*

128. Weiss & Nelson, *supra* note 118.

129. Theodore Friedmann, *Principles for Human Gene Therapy Studies*, 287 SCIENCE 2163-65 (2000).

130. Stolberg, *Biotech Death*, *supra* note 118 (internal quotation marks and citation omitted).

131. Weiss & Nelson, *supra* note 118; Stolberg, *Biotech Death*, *supra* note 118.

plasma ammonia level prior to the infusion of genes and his death.”¹³²

The FDA did not fault the Penn IHGT researchers for their decision to use adults as subjects instead of terminal infants as originally planned.¹³³ We, however, believe that this was the most serious error. Though it is not clear what role other defects of the gene therapy trial played in Gelsinger’s death, it is clear that Gelsinger would not have died if the Penn IHGT researchers had adhered to their original plan of testing the gene therapy treatment on terminal infants. Under the original plan, any deaths to subjects would have been of infants who would have died shortly in any event.

It is obvious to us and, we hope, to the reader, that the Penn IHGT researchers, influenced by Caplan, made the ethically wrong selection of subjects. While this conclusion is easy to draw in hindsight, the ethical and scientific issues were far more clouded while the experiment was pending. Nevertheless, if we evaluate the subject selection decision based on the knowledge that Penn IHGT possessed at the time, it was still the wrong decision.

The Penn IHGT researchers had to choose between a group of subjects that could give fully autonomous consent (adults such as Gelsinger) and a group of subjects for which they could get only substituted consent (terminal infants, whose parents would consent). One can question Caplan’s view that the parents of infants with OTC deficiency inherently could not give informed consent. However, an implicit corollary of Caplan’s position probably has wider appeal: it is better to get informed consent from fully autonomous adult subjects than to get substituted consent from the legal representatives of incompetent subjects. If all else were equal, we would not fault Penn IHGT for following this principle and selecting the subject group that could give fully autonomous consent. But the adults had a worse risk/benefit ratio than the terminal infants. The adults had a great deal more to lose, as the infants would die soon even if not exposed to a potentially toxic treatment. The adults also had less to gain, as the treatment might possibly keep one or more of the infants alive. Penn IHGT could perhaps justifiably assume that the probability of killing an adult subject was very low, and it could certainly assume that the probability of saving an infant subject was very low. Still, from a welfarist perspective, the right choice should have been clear, even in

132. University of Pennsylvania Office of University Commc’ns, *Institute for Human Gene Therapy Responds to FDA* (Feb. 14, 2000), available at <http://www.upenn.edu/pennnews/news/institute-human-gene-therapy-responds-fda> (emphasis added).

133. It might have been difficult for the FDA to find fault with this decision, as the FDA had approved the research protocol. And of course, the FDA did not find fault with Penn IHGT for rejecting the RAC’s recommendation to deliver the virus vector intravenously, since the FDA had prevented Penn IHGT from taking this approach.

advance of Gelsinger's death. Why prefer a small expected harm (adult subjects) to a small expected benefit (terminal infants)? There is no good reason, regardless of whether someone is prepared to consent. The most serious defect of the OTC trial, then, was not too little respect for autonomy (in the sense of lax informed consent), but too much respect for autonomy in the selection of subjects.

B. Do the Regulations Require Selection of the Subject Group with the Best Risk/Benefit Ratio?

We now consider the regulatory provisions on subject selection, using the Gelsinger case as an example. Do the regulations speak to whether the *ethically* correct selection of subjects in the Gelsinger case (terminal neonates, as originally planned, rather than adults) was also *legally* permissible or even mandated? There are special provisions in the HHS regulations regarding research on neonates and children (and the regulations on children have parallel provisions in the FDA regulations).¹³⁴ The use of terminal neonates for the research almost certainly would *not* have violated these regulations, as the research was therapeutic; in terms of the regulations, the research “[held] out the prospect of enhancing the probability of survival of the neonate to the point of viability,”¹³⁵ and “[held] out the prospect of direct benefit for the individual subject.”¹³⁶

Still, the more general provisions of the regulations (subpart A of the HHS regulations, duplicated also in the FDA regulations) also bear on the subject-selection issue in the Gelsinger case. As noted, 45 C.F.R. § 46.111(a) sets forth a list of requirements that must be met before an IRB may approve research. Specifically, 45 C.F.R. § 46.111(a)(1) states the requirement that “[r]isks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.”¹³⁷ The requirement that “[r]isks to subjects are minimized” could be interpreted as a welfarist criterion for subject selection: select those subjects for whom the experiment will be least risky. While in one sense both potential subject groups in the Gelsinger case—terminal infants and adults with a mild form of the disease—faced the risk that they would die as a result of the treatment, in a more important sense the risk of losing future life years was much smaller for the terminal infants, since they would have died anyway. So risks to sub-

134. The Penn IHGT experiment was subject to both the FDA and HHS regulations.

135. 45 C.F.R. § 46.205(b)(1)(i) (2010).

136. HHS, 45 C.F.R. § 46.405; FDA, 21 C.F.R. § 50.52 (2010).

137. HHS, 45 C.F.R. § 46.111(a)(1); FDA, 21 C.F.R. § 56.111(a)(1).

jects were not minimized, on this interpretation, when the investigators decided not to use terminal infants as subjects. On the other hand, section 46.111(a)(1) could be interpreted not as a general injunction to minimize risk, but as an injunction to minimize risk in the choice of procedures. It could be interpreted as bearing solely on the choice of procedures, not on the choice of subjects.¹³⁸

Also relevant is section 45 C.F.R. § 46.111(a)(2). As noted, that section requires that “[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.”¹³⁹ Arguably, risks are not reasonable in relation to benefits if the experiment would be less risky for another class of subjects. Once again, however, this is not a necessary interpretation. While the risk-benefit provision does reflect some paternalism, as previously discussed, the determination of whether the risk to a subject is too high in relation to benefits could be the same whether or not there are other subjects who face lower risks.

Even leaving aside the possibility of using terminal infants as subjects, the entire Penn IHGT study, or the use of Gelsinger as a subject, might have been inconsistent with 45 C.F.R. § 46.111(a)(2). As suggested by opponents of the trial in the RAC, the risks to adult subjects might have been unreasonable in relation to the knowledge to be gained regarding treatment of infants with the disease. Also, Gelsinger might have been an improper subject, under section 46.111(a)(2), because the high level of ammonia in his blood meant that the risk to him was unreasonable in relation to the possible benefits of the study. But assume that the risks to the class of adult subjects, or to Gelsinger alone, were not excessive when measured only against the benefits of the study. HHR regulations could then be interpreted as meaning that it was not improper to select the class of adult subjects, even though another class of subjects had a better risk/benefit ratio.¹⁴⁰ That is not how we would interpret 45 C.F.R. § 46.111(a)(2), but it is a plausible interpretation.

Thus far, 45 C.F.R. § 46.111 seems to give some support, but certainly not conclusive support, to the welfarist approach of choosing the subject class with the best risk/benefit ratio, even when those subjects cannot give autonomous consent. However, 45 C.F.R. § 46.111(a)(3), the only provision that specifically relates to the selection of subjects, points vaguely in the other direction. As noted previously, that provision states the requirement that:

138. As previously noted, there was in fact a separate issue regarding choice of procedures.

139. HHS, 45 C.F.R. § 46.111(a)(2); *see also* FDA, 21 C.F.R. § 56.111(a)(2).

140. HHS, 45 C.F.R. § 46.111(a)(3).

Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.¹⁴¹

In the abstract, the requirement that the selection of subjects be “equitable” might not mean that researchers should select subjects who can give fully autonomous consent over subjects who have a better risk/benefit ratio. To us, such an approach to subject selection would not seem equitable at all. However, the term “equitable,” and even the term “justice,” has taken on a rather tendentious meaning in human subjects research, one which evinces a reluctance to experiment on vulnerable populations. This is largely due to the Belmont Report, which states:

[I]t can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.¹⁴²

A general reluctance to experiment on vulnerable subjects can be justified on welfarist grounds, but not where, as in the Gelsinger case, vulnerable subjects have a far better risk/benefit ratio than fully autonomous subjects.

The regulations do not clearly indicate whether the selection of subjects in the Gelsinger case was legally right or wrong. More generally, while the regulations impose welfarist criteria for the approval of research and the selection of subjects, they do not clearly require the selection of subjects who face lesser risks over those who face greater risks. On subject selection, the regulations go some distance in compromising autonomy for the sake of welfare, but not far enough.

VI. CONCLUSION

As a descriptive matter, autonomy is not an absolute constraint on the pursuit of social welfare through human subjects research in the United States. To a greater extent than is generally recognized, autonomy is compromised for the sake of welfare. Sometimes experiments are done with no consent at all, pursuant to one of the regulatory exceptions to the informed-consent requirement. Sometimes prospective subjects are excluded from a trial for their own welfare, even

141. FDA, 21 C.F.R. § 56.111(a)(3); *see also* HHS, 45 C.F.R. § 46.111(a)(3).

142. Belmont Report, *supra* note 25.

though they are prepared to give informed consent. Patients who want experimental drugs are pressured to enter clinical trials by restrictive drug laws. And the blind clinical trial itself inherently compromises liberal autonomy through the requirement that subjects waive their treatment-related informed-consent rights.

As to some of the areas we have discussed, autonomy is compromised more under the libertarian conception and less under the liberal conception; as to others, autonomy is compromised more under the liberal conception and less (or not at all) under the libertarian conception. Autonomy under the libertarian conception is probably most compromised in subject selection (willing volunteers barred from becoming subjects if they face a risk deemed unreasonable) and in the channeling of patients into clinical trials through restrictive drug laws (the government interposing itself between a willing buyer and willing seller, to serve the interests of third parties). Autonomy under the liberal conception is probably most compromised in the channeling of patients into clinical trials through restrictive drug laws (because the liberal conception of autonomy condemns inducements to participate in an experiment that fall short of actual coercion), and in the emergency-research and minimal-risk exceptions to informed consent (because of liberal autonomy's strong default position against experimentation).

As a normative matter, autonomy *should not* be an absolute constraint on the pursuit of social welfare through human subjects research. For the most part, we endorse the balance between autonomy and welfare set by United States' laws and regulations—which is to say, we endorse the compromise of autonomy for the sake of welfare. The channeling of patients into clinical trials through restrictive drug laws is justified on the convincing assumption that unrestricted access would delay drug trials, resulting in poorer health outcomes overall. The exceptions for emergency research and minimal-risk research are also justified, on the less powerful but still-convincing assumption that they really do increase welfare. The blind clinical trial is so crucial to the advancement of medical knowledge that requiring subjects to waive their treatment-related rights of informed consent as a condition of receiving medical treatment is obviously justified.¹⁴³

It is in the area of subject selection that we demonstrate we do not follow a completely Panglossian approach of endorsing the existing regulatory provisions as welfare-maximizing. We do endorse the paternalistic rule that subjects must be excluded from an experiment if the experiment would pose an unreasonable risk to them. However, the compromise of autonomy in subject selection does not go far

143. Here, few are likely to disagree with our normative conclusion; disagreement is more likely over our analytical argument that the blind clinical trial does represent a compromise of liberal autonomy.

enough. There should be a clearer welfarist directive to prefer the subject group with the superior risk/benefit ratio. Such a directive would have prevented the tragedy of the Gelsinger case; that case demonstrates what can happen when autonomy is not properly subordinated to welfare.